

Preliminary Amendment

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Applicant(s): Stanton et al.

Serial No.: 09/641,801

Confirmation No.: 5388

Filed: August 17, 2000

For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

6	SEQ ID NO:20	Low Enfamil	Colostrum
7	SEQ ID NO:18		SEQ ID NO:3
8			SEQ ID NO:4
9	Low Enfamil		SEQ ID NO:6
9	High Enfamil		SEQ ID NO:5
10			SEQ ID NO:7

* SEQ ID NO:7 < 2 fold difference in titer

** All good inducers

*** No difference in titer

REMARKS

These amendments simply correct typographical errors in the documents referenced or more accurately describe the documents, and add no new matter to the specification.

The amendment to the paragraph spanning pages 8 and 9 provides the current publication number of a PCT document.

The amendment to the paragraph on page 20 corrects the publication number of a PCT document. This PCT document was correctly identified on pages 1 and 9 of the originally filed application.

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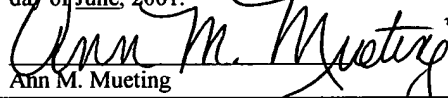
For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR
INDUCING CYTOKINES

The amendments to the tables on pages 26-29 and pages pages 30-31 are to correct inaccuracies in the specification. They are being corrected herein so as not to mislead the Public.

The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

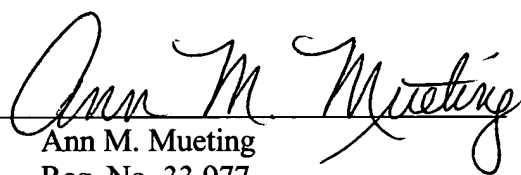
CERTIFICATE UNDER 37 C.F.R. 1.8:

The undersigned hereby certifies that this paper is being deposited in the United States Postal Service, as first class mail, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on this 11 day of June, 2001.


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Appendix A
Specification Amendments with Notations to Indicate Changes Made

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THEREOF FOR INDUCING CYTOKINES

Brackets are used to signify deletions, and underlining is used to signify additions herein.
The changes are also shaded in gray.

Page 8, line 32 to page 10, line 9

Colostrinin has been found to include a number of peptides ranging from 3 amino acids to 22 amino acids or more. These can be obtained by various known techniques, including isolation and purification involving electrophoresis and synthetic techniques. The specific method of obtaining colostrinin and SEQ ID NO:31 is described in International Publication No. WO-A-98/14473. Using HPLC and Edelman Degradation, over 30 constituent peptides of colostrinin have been identified, which can be classified into several groups: (A) those of unknown precursor; (B) those having a β -casein homologue precursor; (C) those having a β -casein precursor; and (D) those having an annexin precursor. These peptides are described in International Patent [Application PCT/GB00/02128] Publication No. WO 00/75173, filed June 2, 2000, claiming priority to June 2, 1999, and can be synthesized according to the general method described in the Examples Section. These peptides (i.e., constituent peptides of colostrinin), which can be derived from colostrinin or chemically synthesized, include: MQPPPLP (SEQ ID NO:1); LQTPQPLLQVMMEPQGD (SEQ ID NO:2); DQPPDVEKPDLQPFQVQS (SEQ ID NO:3); LFFFLPVNVLP (SEQ ID NO:4); DLEMPVLPVEPPFV (SEQ ID NO:5); MPQNFYKLPQM (SEQ ID NO:6); VLEMKFPPPPQETVT (SEQ ID NO:7); LKPFPKLKVEVFPFP (SEQ ID NO:8); VVMEV (SEQ ID NO:9); SEQP (SEQ ID NO:10); DKE (SEQ ID NO:11); FPPPK (SEQ ID NO:12); DSQPPV (SEQ ID NO:13); DPPPPQS (SEQ ID NO:14); SEEMP (SEQ ID NO:15); KYKLQPE (SEQ ID NO:16); VLPPNVG (SEQ ID

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NO:17); VYPFTGPIPN (SEQ ID NO:18); SLPQNILPL (SEQ ID NO:19); TQTPVVVPPF (SEQ ID NO:20); LQPEIMGVPKVKETMVPK (SEQ ID NO:21); HKEMPFPKYPVEPFTESQ (SEQ ID NO:22); SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23); SWMHQPP (SEQ ID NO:24); QPLPPTVMFP (SEQ ID NO:25); PQSVLS (SEQ ID NO:26); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27); AFLLYQE (SEQ ID NO:28); RGPFPILV (SEQ ID NO:29); ATFNRYQDDHGEEILKSL (SEQ ID NO:30); VESYVPLFP (SEQ ID NO:31); FLLYQEPVLGPVR (SEQ ID NO:32); LNF (SEQ ID NO:33); and MHQPPQPLPPTVMFP (SEQ ID NO:34). These can be classified as follows: (A) those of unknown precursor include SEQ ID NOs:2, 6, 7, 8, 10, 11, 14, and 33; (B) those having a β -casein homologue precursor include SEQ ID NOs:1, 3, 4, 5, 9, 12, 13, 15, 16, 17, and 31; (C) those having a β -casein precursor include SEQ ID NOs:18 (casein amino acids 74-83), 19 (casein amino acids 84-92), 20 (casein amino acids 93-102), 21 (casein amino acids 103-120), 22 (casein amino acids 121-138), 23 (casein amino acids 139-156), 24 (casein amino acids 157-163), 25 (casein amino acids 164-173), 26 (casein amino acids 174-179), 27 (casein amino acids 180-201), 28 (casein amino acids 202-208), 29 (casein amino acids 214-222), 32 (casein amino acids 203-214), and 34 (casein amino acids 159-173); and (D) those having an annexin precursor include SEQ ID NO:30 (annexin amino acids 203-220).

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Page 20, line 38 to line 41

Cytokine studies: Colostrinin has previously been shown in the literature to induce IFN- γ and TNF- α , as has Val-Glu-Ser-Tyr-Val-Pro-Leu-Phe-Pro (SEQ ID NO:31), which is disclosed in International Publication No. WO-A-[98/1447] 98/14473. Thus, studies were done to investigate the individual peptides.

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Table at page 26, line 3 to page 29, line 16**Table 2. (cont.) Cytokines induced in human leukocyte cultures stimulated with CCP, colostrum or commercial milk formulas.**

PEPTIDE (Exp. #)	PEPTIDE CONCENTRATION (pg/ml) (mg/ml)	IL-4	IL-6 (pg/ml)	IL-12 (pg/ml)
<u>Example 1</u>				
SEQ ID NO:1	100	0	235.4	0
	10	0	934.8	0
	1	0	675.3	0
	0.1	0	497.1	0
SEQ ID NO:7	100	0	291.3	0
	10	0	645.4	0
SEQ ID NO:8	100	0	1076	0
	10	0	1024	0
	1	0	1013	0
	0.1	0	533.6	0
SEQ ID NO:3	1	0	620.5	0
	0.1	0	107	0
SEQ ID NO:2	100	0	258.6	0
	10	0	551.3	0
	1	0	1205	0
	0.1	0	325	0
SEQ ID NO:4	10	0	1718	0
	1	0	744.4	0

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SEQ ID NO:5	100	0	98.2	0
	10	0	750	0
SEQ ID NO:6	100	0	63.3	0
	10	0	864.5	0
SEQ ID NO:31	100	1.4	1489	0
	10	0	836.3	0
	1	0.4	489.9	0
	0.1	2.4	1635	0
Colostrinin	10	0	1832	0
	1	1.9	1915	0
	0.1	0.4	430.1	0
Raw Colostrum	100	0	1879	0
	10	0	602.2	0
	1	0	1055	0
	0.1	5.0	187.2	0
Control		0	13.5	0
SEA		4	1704	0

Example 2

SEQ ID NO:18	100	0	[142.4]	
0				
SEQ ID NO:19	10	0	[549.7]	0
	1	33.8	[1552]	0
SEQ ID NO:20	100	0	[50]	0
	10	0.4	[105.9]	0

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SEQ ID NO:22	100	41.5	[808.6]	0
	10	32.7	[503.2]	0
	1	30.1	[1005]	0
	0.1	17.8	[396.4]	0
SEQ ID NO:1	100	0	[1471]	0
	10	3.5	[96.5]	5.7
	1	26.6	[626.6]	0
	0.1	47.6	[1385]	0
SEQ ID NO:7	100	24.5	[1546]	0
SEQ ID NO:2	100	22.5	[1292]	33.5
	10	19.9	[1516]	0
	1	10.1	[1886]	9.9
	0.1	29.1	[478.3]	2.2
Enfamil Low Iron	1:5	0.9	[1757]	0
	1:10	4.0	[1958]	0
Enfamil with Iron	1:5	0	[1909]	0
	1:10	0	[ND]	0
Control		0	[183.5]	0
SEA		62.5	[1769]	54.8
<u>Example 3</u>				
SEQ ID NO:1	100	0	942.5	0
	10	ND	ND	ND
SEQ ID NO:7	1	0	32.9	0
	0.1	ND	ND	ND
SEQ ID NO:8	10	0	18.5	4.0
	1	ND	ND	ND

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SEQ ID NO:5	100	0	0	0
Raw	100	0	0	0
Colostrum	10	0	1853	1.6
	1	ND	ND	ND
	0.1	ND	ND	ND
Colostrinin	10	0	2009	17.6
	1	0	1861	7.5
	0.1	ND	ND	ND
SEQ ID NO:31	10	0	16.8	18.7
	1	0	722.9	0
	0.1	ND	ND	ND
SEQ ID NO:22	100	6.0	1630	0
	10	0	46.7	0
	1	0	0	0
	0.1	ND	ND	ND
Enfamil Low Iron	1:5	0	1913	0
Enfamil with Iron	1:5	0.4	1953	0
Control		0	0	0
SEA		16.8	866.2	0

*SEQ ID NOs:1-8 and 31, Raw Colostrum, and Colostrinin were reconstituted on the same day.

*SEQ ID NOs:18, 19, 20, and 22 were reconstituted on the same day.

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Table at page 30, line 1 to page 31, line 24**Table 3. Relative abilities of the various peptides to induce cytokines
and proliferation**

	Ex. 1	Ex. 2	Ex. 1	Ex. 1	Ex. 1	Ex. 2	Ex. 1
Rank	IFN- γ	IFN- γ	Micro. Resp.	Prolif. Resp.	TNF- α	TNF- α	IL-10
1	SEQ ID NO:8	SEQ ID NO:1	SEQ ID NO:8	SEQ ID NO:2	SEQ ID NO:2**	SEQ ID NO:2	SEQ ID NO:8
2	SEQ ID NO:31	SEQ ID NO:2	SEQ ID NO:2	SEQ ID NO:1	SEQ ID NO:8	SEQ ID NO:1	SEQ ID NO:1
3	SEQ ID NO:2	SEQ ID NO:7	SEQ ID NO:31	SEQ ID NO:4	SEQ ID NO:31	SEQ ID NO:7	SEQ ID NO:3
4	SEQ ID NO:1	SEQ ID NO:22	SEQ ID NO:1	Colostrum	Colostrum	SEQ ID NO:22	SEQ ID NO:2
5	SEQ ID NO:3	SEQ ID NO:19	SEQ ID NO:7	Colostrinin	Colostrinin	SEQ ID NO:19	Colostrinin
6	Colistrinin	SEQ ID NO:20	Colostrinin	SEQ ID NO:8	SEQ ID NO:3	SEQ ID NO:20	Colostrum
7	Colustrum	SEQ ID NO:18	Colostrum	SEQ ID NO:31	SEQ ID NO:1	SEQ ID NO:18	SEQ ID NO:31
8	SEQ ID NO:4		SEQ ID NO:3	SEQ ID NO:5	SEQ ID NO:5		SEQ ID NO:4
9	SEQ ID NO:5		SEQ ID NO:4	SEQ ID NO:6	SEQ ID NO:7	Low Enfamil	SEQ ID NO:7
9	SEQ ID NO:6		SEQ ID NO:5	SEQ ID NO:7	SEQ ID NO:4	High Enfamil	SEQ ID NO:5

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10	SEQ ID NO:7	SEQ ID NO:6	SEQ ID NO:3	SEQ ID NO:6	SEQ ID NO:6
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* SEQ ID NO:7 < 2 fold difference in titer

** All good inducers

*** No difference in titer

Table 3. (Cont.) Relative abilities of the various peptides to induce cytokines and proliferation

Rank	Ex. 2 IL-10	Ex. 1 IL-4	Ex. 2 IL-4	Ex. 1 IL-6	[Ex. 2] [IL-6]	Ex. 1 IL-12	Ex. 2 IL-12
1	SEQ ID NO:2	Colostrum	SEQ ID NO:1	SEQ ID NO:31	[Control]	All neg.	SEQ ID NO:2
2	SEQ ID NO:7	Colostrinin	SEQ ID NO:2	SEQ ID NO:8			SEQ ID NO:1
3	SEQ ID NO:1	SEQ ID NO:31	SEQ ID NO:22	SEQ ID NO:1			
4	SEQ ID NO:19		SEQ ID NO:19	Colostrinin			
5	SEQ ID NO:22		SEQ ID NO:7	SEQ ID NO:2			
6	SEQ ID NO:20		Low Enfamil	Colostrum			
7	SEQ ID NO:18			SEQ ID NO:3			
8				SEQ ID NO:4			

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9	Low	SEQ ID
	Enfamil	NO:6
9	High	SEQ ID
	Enfamil	NO:5
10		SEQ ID
		NO:7

* SEQ ID NO:7 < 2 fold difference in titer

** All good inducers

*** No difference in titer
